

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/00	A2	(11) International Publication Number: WO 99/42134 (43) International Publication Date: 26 August 1999 (26.08.99)
(21) International Application Number: PCT/EP99/01154 (22) International Filing Date: 23 February 1999 (23.02.99) (30) Priority Data: 09/027,976 23 February 1998 (23.02.98) US (71) Applicant: BASF CORPORATION [US/US]; 3000 Continental Drive North, Mount Olive, NJ 07828-1234 (US). (72) Inventors: STROH, Friedemann; 16610 Rosa Lane, Southgate, MI 48195 (US). BOWER, David, Kenneth; 2080 Pinetree, Trenton, MI 48143 (US). CHAUNDY, Frederick, Kenneth; 28731 South Point Drive, Grosse Ile, MI 48138 (US). FINNAN, Jeffrey, Lawrence; 727 Beecham Avenue, Dearborn, MI 48124 (US). SOBLESKY, Thomas, B.; 6714 Carlton, Canton, MI 48187 (US). (74) Agent: DÖRPER, Thomas; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).	(81) Designated States: CA, CN, JP, RO, RU, SI, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: SPRAY-DRIED POWDERS WITH HIGH EDIBLE-OIL LOADINGS BASED ON NON-HYDROLYZED GELATIN AND A METHOD OF MAKING SUCH SPRAY-DRIED TABLETTABLE POWDERS (57) Abstract The present invention relates to spray-dried tablettable powders with high edible oil loadings based on non-hydrolyzed gelatin and a method of making such spray-dried tablettable powders. Said edible oils can be vitamin, flavor and fragrance oils.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

Spray-Dried Powders With High Edible-Oil Loadings
Based on Non-Hydrolyzed Gelatin and a Method of Making such
Spray-Dried Tablettable Powders

5

The present invention relates to spray-dried tablettable powders with high edible-oil loadings based on non-hydrolyzed gelatin and a method of making such spray-dried tablettable powders. Said edible oils can be vitamin, flavor or fragrance oils and mixtures

10 thereof.

High potency vitamins, particularly the antioxidant ones, are regularly consumed as the health benefits of these vitamins are increasingly acknowledged in the scientific and lay press.

- 15 However, as the high potency tablets grow larger and larger they approach the limits of swallowability. One way to limit the growth in the size of the tablets is to put more active vitamins with less carriers. To make the oil-soluble vitamins, such as vitamin E, suitable for tableting they must be combined with
- 20 some kind of carrier to form a tablettable powder where the oil does not interfere with tableting. Additionally, the carrier must act as binder with other ingredients within the tablet. Up until now the limit of the content of vitamin E in such carriers has been around 75% (750 international units (IU)/g). However,
- 25 high edible oil (e.g. vitamin E) loading results in tablets with poor characteristics such as low hardness, incomplete disintegration, oil spots on the tablets, oil inhibition of dissolution of trace components in the tablets. The art has attempted to solve the problems with high oil loading tablettable
- 30 powders.

Specifically, US 3,564,097 (Hoffman-La Roche) discloses multivitamin tablets containing high potency vitamin E (35 to 65% by weight) and an inert carrier such as hydrolyzed gelatin.

- 35 Tricalcium phosphate is used as an excipient to enhance stability against cracking and oil bleeding.

US 3,608,083 (Hoffman-La Roche) discloses high potency vitamin E powders having 40 to 60% by weight vitamin E and hydrolyzed

- 40 gelatin. The high potency vitamin E powder is prepared by emulsifying the vitamin E and the hydrolyzed gelatin and then spray drying the emulsion.

US 3,646,192 (Hoffman-La Roche) discloses multivitamin tablets

45 containing high potency vitamin E (35 to 65% by weight) and an inert carrier such as hydrolyzed gelatin. Silica is used as an excipient to enhance stability against cracking and oil bleeding.

US 3,947,596, US 3,959,472, US 3,914,430 and US 3,962,384 (all assigned to Hoffman-La Roche) disclose spray drying processes for preparing a tabletable fat-soluble vitamin powder. The fat-soluble vitamin is about 60% by weight of the powder. Said powder is prepared by blending the fat-soluble vitamin with hydrolyzed gelatin in a sonic homogeneizer (e.g. Homo-Mixer®) to achieve an emulsion having a particle size of 1 to 3 microns. Said emulsion is then spray dried. Further, glidants (silicates) must be introduced into the spray chamber to prevent adhesion of the emulsion particles to the walls of the dryer.

US 3,932,634 discloses an oil soluble vitamin solution comprising 10 to 55% oil soluble vitamins and dispersing agents such as polyoxyethylene sorbitan monooleate and polyethylene glycol 400 monooleate.

US 4,711,894 (assigned to Henkel) discloses a dry free-flowing vitamin E powder comprising 20 to 60% vitamin E and 40 to 80% carrier selected from gelatin (preferably hydrolyzed) silica, starches or gums and a stabilizer selected from hydroxy or amino acids. Said vitamin powder is prepared by spray drying.

US 4,870,196 discloses a method of preparing a free-flowing vitamin E powder by melting the vitamin E and wax and emulsifiers and powdering agents and spraying this mixture to form droplets.

US 4,892,889 (assigned to BASF) discloses a process for making compressible (tabletable) vitamin powders. Said vitamin powder comprises 20 to 60% vitamin E and 6 to 46% non-hydrolyzed gelatin. An effective amount of a carbohydrate such as lactose or corn syrup or mannitol is added to the vitamin/gelatin emulsion, to aid in creating a stable emulsion. Said emulsion is suitable for spray drying to prepare the vitamin powder. Silicon dioxide is injected into the spray drying chamber to improve flowability of the powder.

US 5,120,761 (assigned to BASF) discloses a free flowing spray dried vitamin E powder comprising 50% vitamin E and partially hydrolyzed gelatin.

U.S. 5,478,569 (assigned to Hoffman-La Roche) discloses powdered fat-soluble vitamin compositions comprising approximately 55% vitamin E and fish gelatin. The powder is prepared by spray drying an emulsion of the vitamin and the gelatin. The particle size of the emulsion is about 0.3 μ to 0.6 μ .

Vitamin E for tabletting is generally sold in a powder form. The commercial standard is 500 iu/gram. Vitamin E is 1000 iu/gram in pure form. Therefore, a 500 iu/gram powder consists of 50% vitamin E oil. Recently, however, a powder which comprises 75%
5 vitamin E and carriers such as fish gelatin, calcium silicate and silicon dioxide, is currently sold by Hoffmann-La Roche, Inc. This product has just been made recently available.

Surprisingly, Applicants have improved on the art of high oil
10 loading tabletable powders. Specifically, Applicant's high oil loading tabletable powders are less greasy than currently available products; have better tabletting properties; and the oil loading can be as high as 90% to deliver more active ingredient in a smaller tablet.

15 Also, there are processing advantages to the present invention. At higher loadings of the active ingredient, less carrier is required which leads to cost savings. Since there is less carrier, less water is necessary to dissolve the carrier.
20 Therefore, less energy is necessary to dry the powder and greater throughput is achieved. Because hydrolyzed or partially hydrolyzed gelatin is no longer needed, the extra processing cost and the need to control that processing step is obviated. Finally, the preparation of the present invention can be carried
25 out in a "conventional" spray-dryer, i.e. cool air zone modified spray drying is not necessary because atomized droplet formation is not a problem. Thus, costly equipment modification is also obviated.

30 Gelatin Characterization

Gelatin is most typically characterized by its "Bloom strength". The term "Bloom" as used herein is defined as the weight in grams required to impress a one-half inch diameter plunger 4 mm into a
35 gelatin solution containing 6 percent solids gelled at 10°C for 17 hours. A suitable test procedure for determining bloom is outlined in *Industrial Engineering Chemistry*, Analytical Edition, vol. II, page 348, and vol. XVII, page 64. The maximum Bloom for gelatin is around 300. Three hundred (300) bloom gelatin
40 is commercially available. Also available is "0 bloom" gelatin, which is also known as "hydrolyzed" gelatin. The term "non-hydrolyzed" is herein defined as a gelatin having a bloom number between 30 and 300. Gelatins having the Bloom values between 0 and 300 are also commercially available, e.g. 80, 100 and
45 270 bloom gelatin is currently offered by several manufacturers. Furthermore, the source and the preparation of the gelatin can vary. Sources include gelatin derived from the bone or skin from

bovine or swine and the treatment of the gelatin source can be acid or alkaline followed by boiling in water. Those produced via acid treatment are referred to as Type A and those via alkaline as Type B. More recently gelatin derived from fish has become commercially available. The source and treatment can result in different properties, molecular weight, Bloom strength, as well as its ability to stabilize emulsions.

FLODEX Flowability

10

The term "flowability" as used herein refers to how free flowing a powder is. Specifically, free-flowing powders have a FLODEX® flowability of 50 or more. The FLODEX® flowability test is described in detail in US 5,000,888, column 7, lines 55-70,

15 column 8, lines 1-45, incorporated by reference herein.

Flowability can be measured with the FLODEX® method

(Dow-Lepletit). A sample is placed in a smooth cylinder with a circular hole in the bottom. The whole is closed during filling.

20 Once the complete amount of powder is filled in, the bottom hole is opened. A powder with a good flowability will flow through a small hole, whereas a powder with a poor flowability requires a large hole to leave the cylinder. The FLODEX® value is the reciprocal of the diameter in millimeters times 1,000 of the
25 smallest hole through which the sample will pass. The maximum flowability is obtained in this test utilizing a flow disc having a four millimeter diameter orifice. In this case, the flow obtained is reported as equal to a value of 250. One skilled in the art understands that the value of 250 could imply a higher
30 flowability because the standard flow disc orifice will only measure up to 250.

Malvern Measurement of Droplet Size

35 The oil-droplet size in the powder is measured with a Malvern Mastersizer S® which works on the principle of laser light diffraction. For the measurements, the 300RF lens with an active beam of 2.4 mm is used. The refractive indices used are (1.49, 0.00) for the vitamin E oil and (1.33, 0.00) for the dispersant
40 water. A vitamin E powder or emulsion, about 0.2 g are dispersed in about 20 ml of hot water (50 to 60°C). This dispersion is pipetted slowly in the water of the Small Volume Dispersion Unit (MS1), until the obscuration reaches the desired value of 10 to 30%. The stirrer of the Dispersion Unit is at about 50%.
45 The measurement is evaluated using the Polydisperse Model with a Channels killed setting on the Malvern Mastersizer®. The oil-droplet size distribution of vitamin E powders exhibits

typically two peaks. The first peak has about the same oil-droplet size distribution as the corresponding emulsion. The second peak, the magnitude of which is typically smaller than that of the first peak, is an artifact due to silica used during the spray-drying process. For the oil-droplet size evaluation, we disregard the second peak. The measured oil-droplet size is the D[4,3] (volume averaged diameter) of the first peak. The measurement is always made in duplicate. While the separation of the first and second peak is usually easy for Type A pork skin and Croda SPA® gelatins, for other gelatins the two peaks can be overlapping. In these cases, the two peaks are separated by the minimum or the inflection point (if there is no minimum between the two peaks). If the separation between the peaks is not obvious, we define the first peak as ending at 2 μ .

15

 μ

The term μ as used herein means micron.

Summary

20

The present invention relates to a spray-dried powder containing edible oil-droplets suitable for tableting comprising:

- (a) 40 to 90% edible oil,
- (b) 10 to 60% gelatin

25

wherein further, said edible oil-droplets have an average diameter of $\leq 0.8 \mu$.

30 The present invention also relates to a method of making a spray-dried powder containing edible oil-droplets suitable for tableting comprising:

- (a) 40 to 90% edible oil,
- (b) 10 to 60% gelatin

35

comprising the steps of:

- (a) dissolving said gelatin or a mixture of said gelatins in hot water;
- (b) adding said edible oil to the gelatin in hot water to form an emulsion;
- (c) homogenizing said emulsion formed in step (b) until the average oil-droplet size is ≤ 0.8 ;
- (d) Spray drying the homogenized emulsion from step (c).

40

45

wherein further, said edible oil-droplets have an average diameter of $\leq 0.8 \mu$.

All percentages are weight percent unless otherwise indicated.

- 5 Further, the percentage of edible oil is expressed as dry weight percent.

Detailed description

- 10 The present invention relates to a spray-dried powder containing edible oil droplets suitable for tableting comprising:

- (a) 40 to 90% edible oil,
- (b) 10 to 60% gelatin

15

wherein further, said edible oil-droplets have an average diameter of $\leq 0.8 \mu$.

- The present invention also relates to a method of making a
20 spray-dried powder containing edible oil-droplets suitable for tableting comprising:

- (a) 40 to 90% edible oil,
- (b) 10 to 60% gelatin

25

comprising the steps of:

- (a) dissolving said gelatin or a mixture of said gelatins in hot water;
- 30 (b) adding said edible oil to the gelatin in hot water to form an emulsion;
- (c) homogenizing said emulsion formed in step (b) until the average oil-droplet size is ≤ 0.8 ;
- (d) Spray drying the homogenized emulsion from step (c).

35

wherein further, said edible oil-droplets have an average diameter of $\leq 0.8 \mu$.

- The oil-droplets in the powder or emulsion have an average
40 diameter of less than or equal to 0.8μ , preferably less than or equal to 0.35μ .

All percentages are weight percent unless otherwise indicated.

- Further, the percentage of edible oil is expressed as dry weight
45 percent.

The present invention is prepared by blending the edible oil and the gelatin to form a crude emulsion. Said emulsion is then subjected to high pressure homogenization to achieve the $\leq 0.8\mu$ edible oil-droplet size.

5

The preferred oil-droplet size is 0.05 to 0.8 μ , more preferably 0.1 to 0.4 μ , most preferably 0.25 to 0.35 μ .

At oil loadings larger than 70%, the oil droplet should have an average diameter of less than 0.6 μ , and preferably less than 0.45 μ .

At oil loadings less than 55%, the oil droplet should have an average diameter less than 0.45 μ , and preferably less than 0.35 μ , and most preferably less than 0.30 μ .

While the high-pressure homogenizer is best suited for achieving small oil-droplets on a pilot or plant scale, other types of homogenizers can be used as well. Specifically, a shear-blade agitator results in an emulsion which can be spray dried to a powder having an oil-droplet size of $\leq 0.8 \mu$

Edible Fats and Oils Useful in the Practice of the Present Invention

25

Fats and oils useful in the practice of the present invention include, but are not limited to, flavoring and fragrance oils, vegetable oils, animal fats, and natural and synthetic fat-soluble vitamins selected from A,D,E and K or mixtures thereof. Preferably, the oils are vitamin oils. The most preferred vitamin oils are E and A. Said vitamin oils can be diluted with an inactive oil such as cotton seed, corn or peanut.

For example, vitamin A palmitate is generally sold in powder form as a 500 international units (iu)/gram powder. Vitamin A palmitate in its pure form has a potency of 1.817 X 10⁶ iu/gram. To make a 500 iu/gram powder with a total oil loading of 65% one would use 35% gelatin, 27.5% Vitamin A palmitate, and 37.5% of some inactive oil such as a cottonseed oil or some other similar triglyceride.

To make a vitamin E powder of 800 iu/gram (i.e. 80%,) one would use 80% vitamin E oil and 20% gelatin.

Further, because the market place may still require a 500 iu/gram (50%) vitamin E powder, this can also be achieved by taking advantage of the ease of processing of the present invention.

A powder could be made containing 50% vitamin E oil, 15% vegetable oil, e.g. cottonseed oil, and 35% non-hydrolyzed gelatin. This product could spray drying using no special conditions and with faster drying times than powders at lower total oil loadings. Additionally, the various vegetable oils are seven to ten times less expensive than gelatin. A Vitamin E powder consisting of 50% vitamin E oil and 50% non-hydrolyzed gelatin can be made if the oil droplet size is reduced to less than 0.30 μ .

10

Said edible oils are present at levels of 40 to 90%, more preferably 50 to 80%, and most preferably 65 to 80%.

Gelatins Useful in The Practice of the Present Invention

15

Gelatins useful in the practice of the present invention include, but are not limited to Croda SPA® (45-85 Bloom), derived from specially tanned cow hides, or Type A or Type B derived from bovine skin, bovine bone, pork skin, fish. Said gelatins are present at levels of 10 to 60%, more preferably 20 to 50%, most preferably 20 to 35%.

20

Non-Hydrolyzed gelatins of all species are preferred.

25 Solids Useful in the Practice of the Present Invention

Solids may be optionally added. They may be dissolved or suspended in an oil such as cottonseed oil, corn oil or fractionated triglycerides. For example, beta-carotene

30

and other carotenoids, such as astaxanthin, canthaxantin, beta-apo-8-carotenal, are acceptable solids. The carotenoids are commonly used as suspensions in oil. Furthermore, the solids may be suspended or dissolved in the aqueous phase during processing.

35

Further, some drug active substances are useful solids.

Representative solid pharmaceuticals include, but are not limited to: antiinfectives such as antibiotics, and antiviral agents, analgesics, anorexics, antihelminthics, anti arthritics, antiasthmatics, anticonvulsants, antidepressants, antidiabetic agents, antidiarrheals, antihistamines, antiinflammatory agents, antimigraine preparations, anti nauseaants, antineoplastics, antiparkinsonism drugs, antipruritics, antipsychotics, antipyretics, antispasmodics, anticholinergics, sympathomimetics, xanthine derivatives, cardiovascular preparations including calcium channel blockers, and beta blockers, and anti arrhythmics, antihypertensives, diuretics, vasodilators including general

45

coronary, peripheral and cerebral, central nervous system stimulants, cough and cold preparations including decongestants, hormones such as estradiol, and other steroids, including corticosteroids, hypnotics, immunosuppressives, muscle relaxants, 5 para sympatholytics, psychostimulants, sedatives and tranquilizers. Said pharmaceuticals are suspendible in the oil.

The levels of use of solids is typically 5 to 40% in the oils.

10 Excipients Useful in the Practice of the Present Invention

The term excipient is a catch-all term for diluents or vehicles for an active ingredient. Excipients include: diluents or fillers, binders or adhesives, disintegrants, lubricants, 15 antiadherents, glidants or flow promoters, colors, flavors, sweeteners and adsorbents.

Specifically, tablet fillers are substances that comprise the bulk of the tablet and primarily act as a carrier. Typical 20 tablet fillers include, but are not limited to, calcium sulfate, calcium phosphate, calcium carbonate, starch, modified starches (carboxymethyl starch, etc.), microcrystalline cellulose, lactose, sucrose, dextrose mannitol and sorbitol.

25 Typical levels of tablet fillers are from about 10-90% by weight of the tablet.

Binders act as the "glue" which holds powders together to form granules. Binders include, but are not limited to, natural 30 polymers such as starches or gums acacia, tragacanth and gelatin or synthetic polymers such as PVP and methyl-, ethyl- and hydroxypropylcellulose.

Typical levels of binder levels are from about 1 to 10% of 35 the formulation.

Disintegrants cause compressed tablets to break apart. Typical examples include, but are not limited to, starch, microcrystalline cellulose, purified wool starch, alginic acid, 40 sodium starch glycolate guar gum, crosslinked polyvinyl pyrrolidone (PVP), ion exchange resin and celluloses such as methyl-, sodium carboxymethyl- and hydroxypropylmethyl-.

Typical levels of disintegrant levels are from about 0.5 - 15% 45 of the formulation.

10

Lubricants reduce friction between the granulation and die wall during compression and ejection. Most lubricants are water insoluble and include stearates (magnesium, calcium and sodium), stearic acid, talc and waxes. Water soluble lubricants include

5 PEG's, sodium benzoate, sodium oleate, sodium acetate, sodium lauryl sulfate and magnesium lauryl sulfate.

Typical levels of lubricants are from about 0.25 - 5% of the formulation.

10

Antiadherents prevent sticking to the punch and to the die wall. Typical antiadherents include, but are not limited to, talc, cornstarch, silicon dioxide, sodium lauryl sulfate and metallic stearates.

15

Typical levels of antiadherents are from about 0.1 - 5% of the formulation.

Glidants improve the flow characteristics of the granulation.

20 Typical glidants include but are not limited to, talc cornstarch and silicas.

Typical levels of glidants are from about 0.1 - 5% of the formulation.

25

Colorants are added to help identify types of tablets and for aesthetic purposes. Typical examples include colors designated as D&C and FD&C dyes and lakes.

30 Typical levels of colorants are from about <1% of the formulation.

Flavors and sweeteners are commonly used to improve the taste of chewable tablets.

35

Typical examples include, but are not limited to, natural sugars, aspartame (nondrug approved) and saccharin. Typical usage level is 25 - 50% for natural sugars and of formulation. Typical usage levels for aspartame and saccharin is >1%.

40 Adsorbents are typically silicon dioxides (Syloid, Cab-O-Sil, Aerosil). They retain large quantities of liquids without becoming wet.

Typical levels of adsorbents are from about 1 to 10% of the

45 formulation.

11

See, Handbook of Pharmaceutical Excipients (Academy of Pharmaceutical Science of the American Pharmaceutical Association) and Pharmaceutical Dosage Forms: Tablets edited by Lieberman, Lachman and Schwartz for a detailed description of excipients useful in the practice of the present invention. The following non-limiting Examples 1-19, illustrate how to prepare the high oil loading vitamin E powder suitable for tableting of the present invention.

- 10 Example 20 illustrates how to prepare a vitamin A derivative (13-cis Retinoic acid powder) taking advantage of the ease of processing of the present invention.

Example 1 - Vitamin E-650 with large oil-droplets

- 15 1701 g of non-hydrolyzed Croda SPA® gelatin is dissolved in 6876 g hot water (60°C) using a Gifford-Wood® Rotor-Stator Homogenizer (Model 2L). 3425 g of vitamin E oil (food grade) is added to the solution and emulsified for 10 minutes with the Gifford-Wood® homogenizer. The average oil-droplet size in the emulsion is about 3 μ as measured by the Malvern Mastersizer®. The emulsion is spray dried in a Niro® Utility Spray Drier with centrifugal atomization (wheel speed 12,000 RPM, feed temperature 80°C, air inlet temperature 160°C, air outlet temperature 100°C, feed flow rate 190 g/min). Syloid 74®, silicon dioxide, is added to the spraying chamber as flow aid (1g/min) metered with K-tron® screw feeder.

Example 2 - Vitamin E-650 with small oil-droplets

- 30 The emulsion is prepared as in Example 1, but before spray drying it is passed once through a Niro-Soavi® high-pressure homogenizer (Model 2006) at 1,000 bar pressure drop. The homogenization step results in an average oil-droplet size of 0.43 μ in the emulsion.
- 35 The emulsion is spray dried as in Example 1.

Example 3 - Vitamin E-650 with very small oil-droplets

- The emulsion is prepared as in Example 2 (6626 g water, 1784 g gelatin, and 3590 g vitamin E oil), however, it is passed 4 times through the Niro-Soavi® high-pressure homogenizer (1,000 bar). The homogenization results in an average oil-droplet size of 0.29 μ in the emulsion. The emulsion is spray dried as in Example 1.

12

Example 4 - Vitamin E-700 with very small oil-droplets

The emulsion is prepared as in Example 1 but with higher oil loading (6912 g water, 3853 g vitamin E oil, 1482 g Croda

- 5 SPA® gelatin). The emulsion is passed three times through the Niro-Soavi® high-pressure homogenizer resulting in an emulsion oil-droplet size of 0.28 μ . The emulsion is spray dried as in Example 1.

10 Example 5 - Vitamin E-600 with very small oil-droplets

The emulsion is prepared, homogenized and spray dried as in Example 4 but with lower oil loading (6966 g water, 1951 g Croda SPA® gelatin, 3083 g vitamin E oil). The average oil-droplet

- 15 diameter in the emulsion before spray drying is 0.25 μ .

Example 6 - Vitamin E-550 with very small oil droplets

The emulsion is prepared, homogenized and spray dried as in

- 20 Example 5 but with lower oil loading (7185 g water, 2125 g Croda SPA® gelatin, 2693 g vitamin E oil). The average oil-droplet diameter in the emulsion before spray drying is 0.26 μ .

Example 7 - Vitamin E-500 with very small oil-droplets

25

The emulsion was prepared, homogenized and spray dried as in Example 6 but with lower oil loading (7159 g water, 2338 g Croda SPA® gelatin, 2503 g vitamin E oil). The average oil-droplet diameter in the emulsion before spray drying was 0.26 μ . Since

- 30 only little product is collected at 12,000 RPM (indicating that the limit of sprayability of non-hydrolyzed Croda SPA® gelatin had been reached), the wheel speed was increased to 19,000 RPM.

Example 8 - Vitamin E-750 with very small oil-droplets

- 35 The emulsion was prepared as in Example 4 but with higher oil loading (6575 g water, 4215 g vitamin E oil, 1209 g Croda SPA® gelatin). The emulsion was passed three times through the Niro-Soavi® high-pressure homogenizer resulting in an emulsion oil-droplet size of 0.28 μ . The emulsion was spray dried as in

40 Example 1.

Example 9 - E-650 with non-hydrolyzed type A pork skin gelatin (100 Bloom)

- 45 The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (6501 g water, 1825 g type A pork skin low bloom gelatin, 3674 g vitamin E oil). The average

13

oil droplet diameter in the emulsion before spray drying was 0.32 μ .

Example 10 - E-650 with non-hydrolyzed type A pork skin gelatin
5 (250 Bloom)

The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (8251 g water, 1245 g type A pork skin high bloom gelatin, 2505 g vitamin E oil). The
10 average oil-droplet diameter in the emulsion before spray drying was 0.32 μ .

Example 11 - E-650 with non-hydrolyzed type B bone gelatin
(250 Bloom)

15 The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (7376 g water, 1369 g type B bone high bloom gelatin, 2759 g vitamin E oil) and 5 passes through the high-pressure homogenizer. The average oil-droplet
20 diameter in the emulsion before spray drying was 0.31 μ .

Example 12 - E-650 with non-hydrolyzed type B calf skin gelatin
(220 Bloom)

25 The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (7876 g water, 1535 g type B calf skin high bloom gelatin, 3091 g vitamin E oil). The average oil-droplet diameter in the emulsion before spray drying was 0.43 μ .

30 Example 13 - E-650 with hydrolyzed Croda SPA® gelatin

The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (5660 g water, 1710 g Croda
35 SPA® gelatin, 3445 g vitamin E oil, 7 g Sodium Benzoate, 4 g Potassium Sorbate, 3 g HT Proteolytic 200 in water). After hydrolysis the MW of the gelatin was 15,400. The average oil-droplet diameter in the emulsion before spray drying was 0.32 μ .

40 Example 14 - E-650 with non-hydrolyzed fish gelatin (250 Bloom)

The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (7251 g water, 1576 g fish
45 gelatin, 3173 g vitamin E oil) and 19,000 RPM homogenizer wheel

speed. The average oil droplet diameter in the emulsion before spray drying was 0.33 μ .

Example 15 - E-700 with non-hydrolyzed type A pork skin gelatin
5 (250 Bloom)

The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (7283 g water, 1310 g type A pork skin high bloom gelatin, 3407 g vitamin E oil). The
10 average oil droplet diameter in the emulsion before spray drying was 0.29 μ .

Example 16 - E-700 with non-hydrolyzed type A pork skin gelatin
(275 Bloom)

15 The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (7779 g water, 1172 g type A pork skin high bloom gelatin, 3050 g vitamin E oil). The average oil droplet diameter in the emulsion before spray drying
20 was 0.30 μ .

Example 17 - E-700 with non-hydrolyzed type A bone gelatin
(280 Bloom)

25 The emulsion was prepared, homogenized and spray dried as in Example 4 but with a different recipe (8283 g water, 1310 g type A pork skin high bloom gelatin, 3407 g vitamin E oil). The average oil-droplet diameter in the emulsion before spray drying was 0.29 μ .

30 Example 18 - E-750 with Non-hydrolyzed type A pork skin gelatin
(250 Bloom)

The Emulsion is prepared, homogenized and spray dried as in
35 Example 4 but with a different recipe (7808 g water, 934 g type A pork skin high bloom gelatin, 3258 g vitamin E oil). The average oil droplet diameter in the emulsion before spray drying is 0.30 μ . The resulting powder is analyzed for oil droplet size (0.52 μ), tablet hardness (10 SCU), flowability (Flodex = 84),
40 and tapped density (=0.45 g/cm³).

Example 19 - E-800 with Non-hydrolyzed type A pork skin gelatin
(250 Bloom)

45 The Emulsion is prepared, homogenized and spray dried as in Example 4 but with a different recipe (7715 g water, 787 g type A pork skin high bloom gelatin, 3500 g vitamin E oil), and a

15

different flow aid, Aerosil 200. The potency of the vitamin E oil is 99.3%. The average oil droplet diameter in the emulsion before spray drying is 0.40 μ . The resulting powder is analyzed for oil droplet size (0.50 μ), tablet hardness (5 SCU), flowability

5 (Flodex = 56), and tapped density (=0.44 g/cm³).

Example 20 - 13-cis-Retinoic Acid in oil suspension with Croda® Spa gelatin

- 10 1482 g of non-hydrolyzed Croda SPA® gelatin is dissolved in 6912 g hot water (60°C) using a Gifford-Wood's® Rotor-Stator Homogenizer (Model 2L). 3853 g of 30% 13- cis-retinoic acid micronized in vegetable oil is added to the solution and emulsified for 10 minutes with the Gifford-Wood's® homogenizer.
- 15 The emulsion is passed three times through the Niro-Soavi® high-pressure homogenizer. The emulsion is spray dried as in Example 1.

The spray dried emulsions prepared as described in Examples 1-19, 20 were then evaluated for tabletting. Specifically, the stringent tabletting formulation in Table 1 (in that it relies entirely on the vitamin E powder for binding the tablet together) was used for evaluating the spray-dried formulations of Examples 1-19.

25

TABLE 1

GRAMS/TABLET		
	Ingredient	g/tablet
30	1 Vitamin E Powder 500 to 800 IU/g	0.4000
	2 Syloid™ 244FP	0.0150
	3 Cab-O-Sil™ HS-5	0.0100
	4 Microcel C (calcium silicate)	0.0082

- 35 This tabletting formulation is very good at giving an indication of how well the vitamin E oil is encapsulated. If the oil is not encapsulated, tablets are prone to be spotted and the tablets will be soft. Softness is also dependent on the compressibility of the excipients. These tablets were made on an instrumented
- 40 Manesty B3B Press® with 7/16 standard concave punches at a pressure of 8,000 lbs. The tablets were tested for hardness on a Schleuniger® Model 2E or 4E hardness testers. The hardness values are given in Strong-Cobb Units (SCU). The maximum hardness that can be measured is 64 SCU. Generally, the harder the tablets are
- 45 the better they are. In this formulation a tablet hardness around 10 SCU was considered minimally acceptable.

16

Table 2 illustrates the properties of spray dried high oil loading powders compressed into tablets from the powder formed in Examples 1-19.

5

TABLE 2

PROPERTIES OF SPRAY-DRIED POWDERS FROM EXAMPLES 1 TO 19

EXAMPLE	1	2	3	4	5	6	7	8	9	10
Active Oil Loading (%)	65	65	65	70	60	55	50	75	65	65
Actual Vitamin E-acetate (97%)	67.7	67.7	67.7	72.7	62.5	57.4	53.4	77.7	67.7	67.7
Oil-droplet size-d[4,3](m)	2	0.45	0.29	0.33	0.27	0.27	0.27	0.3	0.37	0.35
Tablet Hardness (SCU)	2	13	40	16	62	>64	>64	6	28	28
Flodex Flowability	38	71	83	100	83	63	38	100	100	56
Tapped Density (g/cm ³)	0.42	0.48	0.53	0.54	0.52	0.55	0.49	0.45	0.52	0.46
Gelatin (%)	29.6	29.6	29.6	24.6	34.8	39.9	43.9	19.6	29.6	29.6
Moisture (%)	2	2	2	2	2	2	2	2	2	2
Silicon dioxide (%)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Actual Potency *IU/g	657	657	657	705	606	557	518	754	657	657

EXAMPLE	11	12	13	14	15	16	17	18	19
Active Oil Loading (%)	65	65	65	65	70	70	70	75	80
Actual Vitamin E-acetate (97%)	67.7	67.7	67.7	67.7	72.7	72.7	72.7	77.7	80.5†
Oil-droplet size-d[4,3](m)	0.34	0.37	0.36	0.36	0.32	0.45	0.35	0.52	0.5
Tablet Hardness (SCU)	23	28	15	31	31	24	22	10	5
Flodex Flowability	71	56	100	50	71	200	100	84	56
Tapped Density (g/cm ³)	0.46	0.51	0.53	0.47	0.47	0.48	0.51	0.45	0.44
Gelatin (%)	29.6	29.6	29.6	29.6	24.6	24.6	24.6	19.6	16.1
Moisture (%)	2	2	2	2	2	2	2	2	1.4
Silicon dioxide (%)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	2
Actual Potency *IU/g	657	657	657	657	705	705	705	754	800†

† The actual potency of the vitamin E oil used in this example is 99.3%

30

Utility of the Present Invention in Tableting

Once the emulsion is spray dried to a powder as described in Examples 1-19, it can be tabletted according to methods known to those skilled in the art. See, Pharmaceutical Dosage Forms, Tablets, 2nd. Ed., 1989, Vols 1, 2, 3, Editors H.A. Lieberman, L. Lachman, J.B. Schwartz

Table 3 herein below illustrates the superior benefit of the present invention over the current technology.

45

17

Table 3

Detailed Comparison of High-Potency Vitamin E powders

5	Characteristic	Example 18 (present invention)	Roche E-75 (current technology)	Example 19 (present invention)
	Vitamin E Powder Potency (iu/gm)	750	750	800
	Ingredient Mixing	No Problems	Mixing of the formulation difficult. Cab-O-Sil separating from rest of mix	No Problems
10	During Tableting	No Problems	Tablets sticking to punches. Pieces of tablets left on tablets. Build up of oily shavings around the top punches	Some powder sticking to upper and lower punches
	Average Compression Force used (lbs)	8073	8195	8267
15	Compression Force Coefficient of Variation-CV (%)	2.8	8.7	3.0
20	Tablet Appearance	Slightly oily on surface but typical. Tablets uniform with no pieces missing.	Tablets oily on surface. Oily wet spots indicate the vitamin E has pressed out. Tablets not uniform with pieces missing	Slightly oily on surface but typical. Tablets uniform with no pieces missing.
	Tablet weight CV (%)	1.2	29.8	0.7
	Tablet Hardness (SCU)	10.3	1.4 (tablets crumbled into powder)	5.3
25	Tablet Hardness CV (%)	8.0	0.89	6.3

The coefficient of variation (CV) is the standard deviation divided by the average multiplied by 100.

30

The results in Table 3 are the average of 10 samples, i.e., 10 tablets were made from the spray dried emulsions prepared in Examples 18 and 19.

35

40

45

WE CLAIM

1. A spray-dried powder containing edible oil droplets
5 comprising:
 - (a) 40 to 90% edible oil,
 - (b) 10 to 60% gelatin
- 10 wherein further, said edible oil droplets have an average diameter of $\leq 0.8 \mu$.
2. A spray-dried powder according to Claim 1, wherein said edible oil is a fat-soluble vitamin or mixtures thereof.
- 15 3. A spray-dried powder according to Claim 1, wherein said gelatin is non-hydrolyzed.
4. A spray-dried powder according to Claim 1, wherein said
20 edible oil content is 50-80%.
5. A spray-dried powder according to Claim 1, wherein said gelatin content is 20-50%.
- 25 6. A spray-dried powder according to Claim 1, wherein said edible oil content is 65-80%.
7. A spray-dried powder according to Claim 1, wherein said said gelatin content is 20-35%.
- 30 8. A spray-dried powder according to Claim 1, wherein said edible oil content is 65-80% and said gelatin content is 20-35%, wherein further said edible-oil droplet has average diameter $\leq 0.35\mu$.
- 35 9. A method for making a spray-dried powder containing edible oil droplets comprising:
 - (a) 40 to 90% edible oil,
 - 40 (b) 10 to 60% gelatin
- wherein further, said edible oil droplets have an average diameter of $\leq 0.8 \mu\text{m}$.

19

Comprising the steps of:

- 5 (a) dissolving said gelatin or a mixture of a said
gelatins in hot water;
- (b) adding said edible oil to the gelatin in hot water
to form an emulsion;
- (c) homogenizing said emulsion formed in step (b), until
the average oil-droplet size is ≤ 0.8 .
- (d) Spray drying the homogenized emulsion from step (c).
- 10 10. A method according to Claim 9, wherein said edible oil is
vitamin E.
11. A method according to Claim 9, wherein said gelatin is
15 unhydrolyzed.
12. A method according to Claim 9, wherein said edible oil
content is 50-80%.
- 20 13. A method according to Claim 9, wherein said gelatin content
is 20-50%.
14. A method according to Claim 9, wherein said edible oil
content is 65-80%.
- 25 15. A method according to Claim 9, wherein said gelatin content
is 20-35%.

30

35

40

45

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/14	A3	(11) International Publication Number: WO 99/42134 (43) International Publication Date: 26 August 1999 (26.08.99)
(21) International Application Number: PCT/EP99/01154 (22) International Filing Date: 23 February 1999 (23.02.99) (30) Priority Data: 09/027,976 23 February 1998 (23.02.98) US (71) Applicant: BASF CORPORATION [US/US]; 3000 Continental Drive North, Mount Olive, NJ 07828-1234 (US). (72) Inventors: STROH, Friedemann; 16610 Rosa Lane, Southgate, MI 48195 (US). BOWER, David, Kenneth; 2080 Pinetree, Trenton, MI 48143 (US). CHAUNDY, Frederick, Kenneth; 28731 South Point Drive, Grosse Ile, MI 48138 (US). FINNAN, Jeffrey, Lawrence; 727 Beecham Avenue, Dearborn, MI 48124 (US). SOBLESKY, Thomas, B.; 6714 Carlton, Canton, MI 48187 (US). (74) Agent: DÖRPER, Thomas; BASF Aktiengesellschaft, D-67056 Ludwigshafen (DE).		(81) Designated States: CA, CN, JP, RO, RU, SI, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 30 September 1999 (30.09.99)
(54) Title: SPRAY-DRIED POWDERS WITH HIGH EDIBLE-OIL LOADINGS BASED ON NON-HYDROLYZED GELATIN AND A METHOD OF MAKING SUCH SPRAY-DRIED TABLETTABLE POWDERS (57) Abstract The present invention relates to spray-dried tablettable powders with high edible oil loadings based on non-hydrolyzed gelatin and a method of making such spray-dried tablettable powders. Said edible oils can be vitamin, flavor and fragrance oils.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01154

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 959 472 A (CANNALONGA MARCO ALFRED ET AL) 25 May 1976 (1976-05-25) cited in the application column 1, line 56 - column 3, line 23 ----	1,2,4,5, 9,10,12, 13
X	US 5 428 569 A (ASANO MASAMICHI ET AL) 27 June 1995 (1995-06-27) cited in the application column 1, line 51 - column 3, line 12; examples 4,7-9 ----	1-5,9-13
A	EP 0 065 193 A (BASF AG) 24 November 1982 (1982-11-24) the whole document -----	1-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

4 August 1999

Date of mailing of the international search report

17/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Engl, B

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/01154

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3959472 A	25-05-1976	AT 353232 B	12-11-1979
		BE 797921 A	09-10-1973
		CH 586568 A	15-04-1977
		DE 2317434 A	06-12-1973
		FR 2179899 A	23-11-1973
		GB 1422974 A	28-01-1976
		JP 987059 C	21-02-1980
		JP 49007415 A	23-01-1974
		JP 54018331 B	06-07-1979
		NL 7304921 A	12-10-1973
		US 3947596 A	30-03-1976
		US 3914430 A	21-10-1975
		US 3962384 A	08-06-1976
US 5428569 A	27-06-1995	JP 2716906 B	18-02-1998
		JP 6028899 A	04-02-1994
		DE 4309814 A	30-09-1993
		KR 9605893 B	03-05-1996
EP 0065193 A	24-11-1982	DE 3119383 A	02-12-1982
		AT 16814 T	15-12-1985
		AU 553623 B	24-07-1986
		AU 8372582 A	18-11-1982
		CA 1202809 A	08-04-1986
		DK 216082 A,B,	16-11-1982
		DK 334188 A,B,	17-06-1988
		JP 1670100 C	12-06-1992
		JP 3035347 B	27-05-1991
		JP 57195161 A	30-11-1982
		US 4522743 A	11-06-1985